Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev with the Tandem t:slim X2 with Control-IQ in Adults, Adolescents and Children with Type 1 Diabetes

TL1 Study

Statistical Analysis Plan

Version History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Protocol Version	Author	Approver	Effective Date	Study Stage
1.0	4.0	Ryan Bailey	Peter Calhoun	June 28th, 2022	Planning, enrollment has not started.
2.0	4.0	Ryan Bailey	Peter Calhoun	October 20th, 2022	Enrollment
3.0	4.0	Ryan Bailey	Peter Calhoun	March 1st, 2023	Enrollment
4.0	4.0	Ryan Bailey	Peter Calhoun	August 25th, 2023	Enrollment and Follow-up complete.

Version Number	Revision Description
1.0	Original Version
2.0	Added sub-group analysis by open-loop basal rates. Add analyses for the trial level safety review.
3.0	Clarified that periods following meal and exercise challenges would not be used to calculate insulin metrics. Added that screening HbA1c could be used in place of central lab HbA1c at baseline if the central lab value is missing. Added analysis windows for HbA1c and PRO outcomes. Specified requirements for calculating insulin metrics.
4.0	Added that summary statistics for all safety and exploratory endpoints will be tabulated separately for pediatric and adult participants. Clarified that for meal and exercise challenges CGM and insulin metrics will be calculated for hours 3-5 after the start of the meal challenges and hours 2-4 after the start of the exercise challenge. Clarified that for subgroup analyses the Humalog period total daily insulin will be used. Added new metrics related to infusion site reactions. Added analyses for pump settings and infusion set change intervals.

Approvals

Role	Digital Signature or Handwritten Signature/Date
Author: Ryan Bailey	Ryan Bailey I agree to the terms defined by the placement of my signature in this document 2023-08-25 14:05-04:00
JCHR Senior Statistician: Peter Calhoun	Peter Calhoun I agree to the terms defined by the placement of my signature in this document 2023-08-25 14:11-04:00
JCHR Coordinating Center Director: John Lum	John Lum I am digitally signing this document 2023-08-25 14:26-04:00
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Contents

1 Consistency of Statistical Analysis Plan with Protocol

All analyses listed in this document are consistent with study protocol (version indicated on the version history table).

2 Study Overview

The Tandem t:slim X2 pump with Control-IQ technology is a closed loop automated insulin delivery system approved by FDA. Lyumjev™ is a rapid acting human insulin analog that has been shown to improve glycemic control in adults with diabetes. This document outlines the statistical analyses to be performed for a clinical trial evaluating the impact of Lyumjev used with the Control-IQ system.

The study population includes individuals ages 6 to <81 years old with a diagnosis of type 1 diabetes for at least 1 year who are currently using Control-IQ technology. This is a prospective, single arm study.

3 Statistical Hypothesis

The primary objective of the study is assessment of safety. Severe hypoglycemia and diabetic ketoacidosis (DKA) event rates will be compared with previously published data from the T1D Exchange registry, which reported the frequency of 1 or more severe hypoglycemia and DKA events in the prior 3 months according to age group (Table 1 in Section 15). The following two hypotheses will be tested:

Severe Hypoglycemia:

- *Null Hypothesis*: There is no difference in the proportion of study participants who experience a severe hypoglycemic event while using Lyumjev with Control-IQ technology compared with those in the T1D Exchange registry matched by age cohort.
- *Alternative Hypothesis:* There is a nonzero difference in the proportion of study participants who experience a severe hypoglycemic event while using Lyumjev with Control-IQ technology compared with those in the T1D Exchange registry matched by age cohort.

Diabetic Ketoacidosis:

- *Null Hypothesis*: There is no difference in the proportion of study participants who experience a diabetic ketoacidosis event while using Lyumjev with Control-IQ technology compared with those in the T1D Exchange registry matched by age cohort.
- *Alternative Hypothesis:* There is a nonzero difference in the proportion of study participants who experience a diabetic ketoacidosis event while using Lyumjev with Control-IQ technology compared with those in the T1D Exchange registry matched by age cohort.

4 Sample Size

A sample size of 160 completers was determined to provide reasonable precision for assessing safety endpoints and is not based on statistical principles. Up to 200 participants will be enrolled in the trial so that at least 160 complete the trial. We will aim to enroll approximately 80 participants between 6 and 13 years old and approximately 80 participants ages 14 and older, with at least 20 participants between 14 and 17 years old. A study wide goal will aim to have at least 33% of trial completers with a screening HbA1c ≥7.5% and at least 10 completers with a baseline insulin rate >3 units/hour.

5 Endpoints

5.1 Key Safety Endpoints

- Severe hypoglycemia
- Diabetic ketoacidosis
- Unanticipated adverse device effects (UADE)
- Other serious adverse events
- Adverse drug reactions

5.2 Secondary Safety Endpoints

- All reportable adverse events
- CGM hypoglycemia outcomes: overall and during postprandial periods for announced meals, excluding meal challenges described separately below
  - % time <54 mg/dL
  - % time <70 mg/dL
  - Rate of hypoglycemia events, defined as 15 or more consecutive minutes <54 mg/dL (overall only)

5.3 Exploratory Endpoints

CGM Metrics: overall and during daytime, nighttime, and postprandial periods

- % time in range 70-180 mg/dL, % time >180 mg/dL, % time >250 mg/dL, and % time in range 70-140 mg/dL
- Mean glucose
- Glycemic coefficient of variation (CV) and glycemic standard deviation (SD)
- Rate of hyperglycemia events, defined as 90 or more minutes >300 mg/dL within 120 minutes (overall, daytime, and nighttime only)
- Postprandial incremental area under the glucose curve (postprandial period only)
- Peak postprandial glucose (postprandial period only)
- % time <54 mg/dL, % time <70 mg/dL, and rate of hypoglycemic events, defined as 15 or more consecutive minutes <54 mg/dL (daytime and nighttime only)

HbA1c Metrics

- HbA1c change from baseline

Insulin Metrics: overall and during daytime, nighttime, and postprandial periods, calculated per day or per meal as appropriate

- Average bolus insulin
- Average manual bolus insulin
- Average automated bolus insulin
- Average basal insulin
- Average total insulin

System Use: overall

- % CGM use
- % Closed loop use
- % Time in different operational modes

Patient Reported Outcomes

- TRIM-Diabetes (TRIM-D)
  - Total Score
  - Treatment Burden Subscale
  - Daily Life Subscale
  - Diabetes Management Subscale
  - Compliance Subscale
  - Psychological Health Subscale
- Trim-Diabetes Device (TRIM-DD)
  - Total Score
  - Device Function Subscale
  - Device Bother Subscale
- Insulin Treatment Satisfaction Question (ITSQ)
  - Total Score
  - Inconvenience Subscale
  - Lifestyle Subscale
  - Hypoglycemic Control Subscale
  - Glycemic Control Subscale
  - Delivery System Subscale

6 Calculation of Endpoints

6.1 Safety Endpoints

An event is defined as a severe hypoglycemic event if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

An event is classified as a DKA event if the following occur:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.24 or serum bicarbonate (or CO2) <15; and
- Treatment provided at a health care facility

For each of the endpoints listed in Section 5.1, the total number of events for each participant and the event rate per 100 person years will be calculated. Event rates will be calculated as the total number of events occurring after the start of the treatment period divided by the number of person years the participant was active in the study. The person years will be calculated as the number of days between the start of treatment period and either the 13-week visit date or drop out date divided by 365.25.

The proportion of participants with at least 1 or more severe hypoglycemia and DKA events will be compared with published T1D Exchange data matched by age group (<18 years and ≥18 years) (Table 1). An overall proportion will also be compared with the expected proportions from the T1D Exchange population using weights derived from the age groups. Study endpoint will be met if severe hypoglycemia and DKA event rates are not significantly higher during follow-up compared with T1D Exchange frequency.

A sensitivity analyses will restrict to severe hypoglycemic events occurring during the treatment period which resulted in a seizure or loss of consciousness, and DKA events which resulted in inpatient hospitalization or prolongation of existing hospitalization.

Adverse events occurring in the treatment phase during periods where Humalog is used will be reported separately.

6.2 CGM Endpoints

CGM metrics will be computed for three study periods: (1) Pre-study period, (2) Lead-in period, and (3) Treatment period. Metrics will be calculated over 24 hours, during the daytime (6:00 AM to 11:59 PM) and nighttime (12:00 AM to 5:59 AM) periods, and during postprandial periods. CGM data from periods during the treatment phase where Humalog is used will not be included in the calculation of CGM metrics.

CGM metrics during pre-study period will be computed when possible using 28 days of pre-study CGM data collected at enrollment. CGM metrics for the lead-in period will be calculated by pooling all CGM data collected in the last 16 days of the lead in period. If multiple lead-in periods were required, CGM metrics will only be computed for the most recent. Data collected from the start of the treatment period until the date of the 13-week visit will be used to calculate CGM metrics during the treatment period. For those who miss the 13-week visit, data collected from the start of the treatment period to the last date that data is available or 91 days after the start of the treatment period, whichever comes first, will be used to compute CGM metrics. At least 24 hours of CGM data during overall, daytime, nighttime, and postprandial periods must be available for metrics to be calculated during those periods. CGM metrics will not include daytime and following nighttime CGM readings on days with meal or exercise challenges; these will be analyzed separately as described in Section 8.4.

6.2.1 Details for Postprandial Periods Not Associated with Meal Challenges

The start time of a meal is defined as the time a carbohydrate is entered into the study pump. CGM data collected in the 4 hours following the start of the meal will be used to compute

postprandial CGM metrics. If another carbohydrate is entered less than 4 hours after the carb entry, then data collected up until the following carb entry will be used to compute CGM metrics. Meals are defined as the 3 largest carb entries on a calendar day. All postprandial CGM data will be pooled for each participant when calculating CGM metrics, and metrics will be calculated separately for the lead-in and treatment periods.

Postprandial % time <54 mg/dL and % time <70 mg/dL will be computed using all postprandial data and data ≤1, ≤2, >1 to ≤2, and >2 to ≤4 hours following a meal. All data within these bins will be pooled across meals for each participant prior to calculating % time <54 mg/dL and % time <70 mg/dL.

Postprandial incremental area under the curve (iAUC) will be calculated using the trapezoidal method [1]. For each meal the baseline value will be set equal to the most recent CGM glucose measurement prior to the carb entry. If the most recent measurement occurred more than 15 minutes prior to the carb entry than baseline glucose for that meal will be considered missing and postprandial iAUC will not be calculated. At least 3 hours of CGM data in the 4-hour postprandial period must be available to calculate iAUC. For each participant the iAUC calculated for each meal will be averaged. This will be done separately for the lead-in and treatment periods.

6.2.2 CGM Use

The percentage of time using CGM will be calculated during the treatment period by dividing the amount of time the CGM was used by the total follow-up time in the period. The amount of CGM use will be determined based on the number of readings available (each reading represents 5 minutes of use). Readings taken from 12:00 AM on the day after the baseline visit until 11:59 PM on the day prior to the date of the 13-week visit will be used to calculate CGM use for participants who complete the study. For participants dropped from the study, readings taken from 12:00 AM on the day after the baseline visit until 11:59 PM on the date prior to study withdrawal will be used to calculate CGM use.

6.2.3 CGM Endpoints Following Meal and Exercise Challenges

Participants will complete 1 meal and 1 exercise challenge during the lead-in period and 3 meal and exercise challenges during the treatment period. The following CGM metrics will be computed before, during, and after meal and exercise challenges:

- Time in Ranges 70-180 mg/dL, 70-140 mg/dL, >180 mg/dL, >250 mg/dL
- Mean Glucose
- Glucose CV
- Glucose SD
- Peak Glucose (meal challenge only)
- Nadir Glucose (exercise challenge only)
- Postprandial iAUC (computed for 3 hours following meal challenges only, following the method described in Section 6.2.1)
- The proportion of participants with at least one CGM hypoglycemic event < 54 mg/dL
- The proportion of participants with at least one CGM value < 70 mg/dL

- Time in ranges < 70 mg/dL, <54 mg/dL (overnight period only)

For meal challenges, CGM data collected between the start of the challenge and 3 hours following the start, between 3 hours after the start of the challenge and 5 hours after the start of the challenge, and in the overnight period (12 AM to 5:59 AM) on the following day will be used to compute CGM metrics. The times provided in the study logbook will be used as the start and end times of the meal challenge. Metrics will be computed separately for each of the 3 meal challenges during the treatment period. At least 75% of CGM data must be available in each period for metrics to be analyzed for that period.

For exercise challenges, CGM data collected between the start of the challenge and 2 hours after the start, between 2 hours after the start of the challenge and 4 hours after the start of the challenge, and in the overnight period (12 AM to 5:59 AM) on the following day will be used to compute CGM metrics. Metrics will be calculated separately for each of the 3 exercise challenges during the treatment period. At least 75% of CGM data must be available in each period for metrics to be analyzed for that period.

6.3 Insulin Endpoints

The insulin metrics listed in Section 5.3 will be calculated during the lead-in period and treatment period. The sum of basal, bolus, and total (basal+bolus) insulin delivered will be calculated on each calendar day, and then averaged within each study period to calculate the average daily insulin doses. Average daily insulin doses will be divided by the participants weight (in kg) to get the dose in units/kg. Metrics will be calculated over 24 hours, during the daytime (6:00 AM to 11:59 PM) and nighttime (12:00 AM to 5:59 AM), and after meal and exercise challenges. At least 20 hours of basal insulin data will be required on a given day for 24-hour metrics to be calculated, at least 15 hours are required for daytime metrics, and at least 5 hours are required for nighttime metrics. At least 1 day with sufficient insulin data is required during a period to calculate insulin metrics for that period. 24-hour, daytime, nighttime, and post-prandial insulin metrics will not include daytime and following nighttime insulin data on days with meal or exercise challenges; these will be analyzed separately. Insulin data from periods during the treatment phase where Humalog was used will not be included in the calculation of insulin metrics.

6.3.1 Insulin Endpoints during Post-Meal Periods Not Associated with Meal Challenges

For each participant the average postprandial basal, bolus, and total insulin will be calculated. Insulin data collected in the 4 hours after a meal will be used to calculate insulin metrics for that meal. At least 3 hours of insulin data must be available during the postprandial period for metrics to be calculated. If another carb entry occurs within 4 hours of the meal, then insulin data collected until the next carb entry will be used. The sum of basal, bolus, and total (basal+bolus) postprandial insulin delivered will be calculated on each calendar day, and then averaged within each study period to calculate average daily postprandial insulin metrics.

6.3.2 Insulin Endpoints Following Meal and Exercise Challenges

For each meal and exercise challenges the amount of basal, bolus, and total insulin delivered will be calculated for each participant. Insulin metrics will be computed for the same time periods discussed in Section 6.2.3. At least 75% of insulin data must be available during the challenge for metrics to be calculated. Insulin metrics will be calculated separately for each of the 3 meal and exercise challenges occurring during the treatment period. The start and end times of the meal and exercise challenges will be determined from the study logbooks.

6.4 Closed Loop Use

The percentage of time the control IQ system was used in closed loop mode during the treatment period will be calculated. This will be done by summing the total amount of time in closed loop mode from 12:00 am the day after the training visit to 11:59 pm on the day prior to the 13-week visit and dividing by the total follow-up time. For participants who drop from the study, data between 12:00 am on the day after the training visit to 11:59 pm on the day prior to study withdrawal will be used to calculate closed loop use. The same will be done for open loop, exercise, and sleep modes.

6.5 Patient Reported Outcomes

6.5.1 TRIM-D and TRIM-DD

In the TRIM-D and TRIM-DD questionnaires all items are scored on a 5-point Likert scale. For the total score and subscale scores, a raw score will first be calculated by summing across items. Raw scores are then transformed to a 0 to 100 scale by using the following formula:

$$\frac{Raw\ Score - Lowest\ Possible\ Raw\ Score}{Range\ of\ Possible\ Raw\ Scores} \times 100$$

If any items are unanswered the total score and subscale pertaining to that item will not be calculated.

6.5.2 ITSQ

Items on the ITSQ are scored on a 7-point Likert scale. The raw total score and subscale scores are computed by calculating the mean across all non-missing item scores. Scores are then transformed to a 0 to 100 scale by using the following formula:

$$\frac{7 - Raw\ Score}{6} \times 100$$

At least 75% of items must be non-missing to calculate scores.

7 Analyses Cohorts

All participants who initiate the treatment and provide at least 24 hours of CGM data will be included in the analyses.

7.1 Analysis Windows

The central lab HbA1c measured at the end of the lead-in period must be collected within 21 days before to 7 days after the Lyumjev training visit, and the HbA1c measured at the end of the

treatment period must be collected within 42 days before to 30 days after the 13-week target date (91 days after the Lyumjev training visit). HbA1c measurements collected outside the analysis windows will be treated as missing.

The PRO outcomes at screening must be collected prior to the Lyumjev training visit, and PRO outcomes at 13 weeks must be collected within 42 days before to 30 days after the 13-week target date (91 days after the Lyumjev training visit). PRO outcomes collected outside the analysis windows will be treated as missing.

8 Statistical Analyses

8.1 Key Safety Analyses

The total number of events, number and proportion of participants who experienced at least one event during the treatment period and the rate of events per 100 person years will be tabulated for each outcome listed in Section 5.1. The proportion of SH and DKA events will be compared to proportions of events occurring in a similar time frame among participants enrolled in the T1D exchange. These proportions have been previously published [2].

Barnard's exact test will be used to test the difference in proportions. A two-sided p-value testing the null hypothesis of no difference in proportions will be reported. For unanticipated adverse device effects, adverse drug reactions, and serious adverse events, the total number, number and proportion of participants who experienced at least one event during the treatment period and the rate of events per 100 person years will be tabulated.

All analyses described in this section will be repeated restricting to only severe hypoglycemic events that were associated with a seizure or loss of consciousness. Summary statistics will be reported for key safety outcomes by age group (6-13, 14-17, 18-25, 26-49, ≥50).

8.2 Secondary Safety Analyses

The total number of any type of adverse event, number and proportion of participants who experienced at least one adverse event during the treatment period and the rate of adverse events per 100 person years will be tabulated. For the CGM metrics listed in Section 5.2, summary statistics for each metric will be reported during the pre-study, lead-in, and treatment periods. The main analyses will compare metrics from the lead-in period to the treatment period, and additional analyses will compare the pre-study period to the treatment period. Linear mixed models including study visit as a fixed effect and clinical site as a random effect will be used to estimate the mean change from the lead-in period to the treatment period. Similar models will be used to estimate the change from the pre-study period to the treatment period. A point estimate, two-sided 95% confidence interval and two-sided p-value will be reported from the models. If residuals are highly skewed, then a transformation or non-parametric method will be used. Summary statistics for all secondary safety endpoints will be tabulated separately for pediatric and adult participants, and by more detailed age groups (6-13, 14-17, 18-25, 26-49, ≥50).

8.3 Exploratory Analyses

Linear mixed models including study visit as a fixed effect and clinical site as a random effect will test the change from the lead-in period to the treatment period for all exploratory CGM, insulin, and HbA1c endpoints. If a central lab HbA1c is not available at baseline the screening HbA1c will be used. Similar models will test the change from screening to the end of the treatment period for patient reported endpoints. A point estimate, two-sided 95% confidence interval and two-sided p-value will be reported from the models. If residuals are highly skewed, then a transformation or non-parametric method will be used. For CGM metrics, a similar model will be used to test differences between the pre-study period and the treatment period. All analyses will be replicated for daytime, nighttime, and postprandial CGM metrics. A sensitivity analyses will compare all 24 hour CGM metrics between the lead-in and treatment periods restricting to complete cases. Summary statistics for all exploratory endpoints will be tabulated separately for pediatric and adult participants and by more detailed age groups (6-13, 14-17, 18-25, 26-49, ≥50).

8.4 Meal and Exercise Challenges

Linear mixed models similar to those described in Section 8.3 will be used to test the change from the lead-in period to the treatment period in CGM and insulin metrics calculated during meal challenges where no bolus was taken. Summary statistics will be reported for metrics calculated during meal challenges where a half or full bolus was taken. The percentage of meal or exercise challenges with a hypoglycemic event will be calculated, but the % time <54 mg/dL and % time <70 mg/dL will not be computed due to the short timeframe. A similar model will compare metrics between the lead-in and treatment periods for exercise periods, and linear contrasts will be used to test the null hypotheses that metrics for all 3 exercise periods during the treatment period are not different from the metrics calculated during lead-in period. For binary outcomes, repeated measures logistic regression model will be used to compare lead-in and treatment periods. Summary statistics for all meal and exercise challenge endpoints will be tabulated separately for pediatric and adult participants and by more detailed age groups (6-13, 14-17, 18-25, 26-49, ≥50).

8.5 Protocol Adherence and Retention Analysis

The following outcomes relating to protocol adherence and retention will be reported. Summary statistics appropriate to the distribution will be tabulated.

- A flowchart reporting the following:
  - Number of participants enrolled
  - Number of participants who completed the Humalog training visit
  - Number of participants who completed the Lyumjev training visit
  - Number of participants who completed/missed the 6-week visit
  - Number of participants who completed/missed the 13-week visit
  - Number of participants who dropped from the study between each visit
- Reasons for dropouts
- Number of protocol deviations

- Number of and reasons for unscheduled visits and contacts

9 Baseline Descriptive Statistics

At the initiation of the treatment period summary statistics appropriate to the distribution will be tabulated for the following characteristics:

- Age
- Diabetes duration
- HbA1c at screening
- Sex
- Race/ethnicity
- Highest level of education
- Annual household income
- Type of insurance
- Body Mass Index (BMI)
- Number of hypoglycemic events that involved a seizure or loss of consciousness in the 12 months prior to screening
- Number of DKA events in the 12 months prior to screening
- Daily SMBG Checks based on device downloads
- Length of Control IQ use
- Type of insulin used with control IQ prior to treatment period
- Number of non-insulin glucose lowering medications

10 Additional Analyses

Summary statistics appropriate to the distribution will be tabulated for the following outcomes during the treatment period:

10.1 Device Issues

- Total number of device issues, overall and by issue type
- Number of occlusion alarms which prompted an infusion set change.

10.2 Infusion Site Reactions

The following metrics will be tabulated separately for the lead-in and treatment periods.

- Number of infusion site reactions (number of events and number of participants with ≥ 1 event).
- Number of infusion site reactions resulting in an adverse event.
- Number of infusion site reactions resulting in study discontinuation.
- Number of infusion site reactions per participant
- Number of infusion site reactions per study week
- Total number of each type of reaction (erythema, induration, site pain, pruritis, edema) overall and by reaction severity (mild/moderate or severe). The total number of events and number of participants with ≥1 event will be tabulated.

The following metrics will be tabulated in the treatment period and tabulations will be stratified by reaction type (erythema, induration, site pain, pruritis, edema). Tabulations will further be stratified by pediatric and adult participants and by reaction severity (mild/moderate or severe).

- Duration of infusion site reaction
- Timing of reaction relative to Lyumjev insulin administration
- Location of infusion site reaction

10.3 Open-Loop Basal Rates

Participants will be split into subgroups based on whether the open-loop basal rate exceeds ≥3 U/hr for at least part of the day during the lead-in period. Summary statistics for mean glucose, time in range 70-180 mg/dL, time in range 70-140 mg/dL, time > 180 mg/dL, time > 250 mg/dL, glucose SD, glucose CV, time < 70 mg/dL, and time < 54 mg/dL will be reported within these subgroups. A listing of outcomes in each period will be provided for participants who set the open-loop basal rate to ≥3 U/hr.

10.4 Pump Settings

Summary statistics for the profile basal rate (U/day), carb ratio, and insulin sensitivity factor (ISF) will be tabulated for week 1, week 13, and the change from week 1 to week 13. If different carb ratio or ISF settings are used within a given week, then a weighted average will be calculated based on the length of time each setting was used.

10.5 Infusion Set Changes

Appropriate summary statistics for the interval between infusion set changes will be tabulated. The intervals between infusion set changes will be categorized and the number and percentage in each category will be tabulated separately for the lead-in and treatment periods. Tabulations will be reported for the overall cohort and separately for pediatric and adult participants.

The mean number of infusion set changes per week will be calculated on a participant level and compared between the Humalog and Lyumjev periods using a linear mixed model with clinical site included as a random site effect. If residuals are skewed, then a transformation or non-parametric method will be used.

11 Subgroup Analyses

Descriptive analyses of all safety, HbA1c, 24 hr-CGM and insulin outcomes will be performed within age groups (6-12, 14-17, 18-25, 26-49, ≥50). Additionally, time in range 70-180 mg/dL and time <54 mg/dL during lead-in and treatment periods will be compared within the following subgroups:

- Age
- Diabetes duration
- Education
- Sex
- Race/Ethnicity

- HbA1c at Screening
- Pre-study CGM time in range 70-180 mg/dL
- Humalog lead-in total daily insulin

For each subgroup the mean difference and 95% CI will be reported within each group. Interactions between the subgroup and change from the lead-in to treatment period will be assessed using repeated measures mixed effects linear regression models with subgroup, visit, and a subgroup by visit interaction term included as fixed effects and clinical site included as a random effect. If the subgroup variable is measured on a continuous scale, then the continuous version will be included in the model. Two-sided p-values for interaction will be reported.

12 Trial Level Safety Review

A trial level safety review will be conducted when participants have been followed for a combined 10,000 hours. Summary statistics will be tabulated for key safety endpoints listed in Section 5.1, device issues (Section 10.1), and infusion site reactions (Section 10.2). Listings with descriptions of each event will be provided.

13 Multiple Comparisons

The key safety endpoints will not be corrected for multiple comparisons. For all other endpoints, confidence intervals and p-values reported will be adjusted using the adaptive two stage group Benjamini-Hochberg (TST GBH) method to maintain a false discovery rate of 0.05 [3]. For multiplicity adjustments outcomes will be grouped as follows:

- Secondary safety endpoints
- HbA1c, 24 hour, daytime, nighttime, and postprandial CGM outcomes (Lead-In vs. Treatment)
- 24 Hour, daytime, and nighttime CGM outcomes (Pre-Study vs. Treatment)
- CGM outcomes following meal and exercise challenges
- 24 hour, daytime, nighttime, postprandial insulin metrics
- Insulin outcomes following meal and exercise challenges
- Subgroup analyses
- Patient reported outcomes

14 References

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15 T1D Exchange Published Table (doi: 10.1089/dia.2018.0384)

Table 1. Frequency of Acute Complications in the 2016-2018 T1D Exchange Registry Cohort

	6–12 years old		13–17 years old		18–25 years old		26–49 years old		≥50 years old	
	N	# ≥ 1 Event (%)	N	# ≥ 1 Event (%)	N	# ≥ 1 Event (%)	N	# ≥ 1 Event (%)	N	# ≥ 1 Event (%)
Frequency of ≥1 Severe Hypoglycemia Event in Prior 3 Months [a]										
Overall	1313	62 (5%)	3183	155 (5%)	2445	138 (6%)	2143	157 (7%)	1976	189 (10%)
Insulin Delivery Method										
Pump	973	39 (4%)	2134	67 (3%)	1585	78 (5%)	1442	85 (6%)	1243	114 (9%)
Injections	317	22 (7%)	967	83 (9%)	817	58 (7%)	656	71 (11%)	706	74 (11%)
CGM Status										
CGM user	414	14 (3%)	584	15 (3%)	424	17 (4%)	684	36 (5%)	577	39 (7%)
CGM non-user	899	48 (5%)	2599	140 (5%)	2021	121 (6%)	1459	121 (8%)	1399	150 (11%)
Most Recent HbA1c										
<7.0% (<53 mmol/mol)	96	4 (4%)	174	8 (5%)	257	11 (4%)	575	37 (6%)	498	51 (10%)
7.0-<7.5% (53-<58 mmol/mol)	148	4 (3%)	268	9 (3%)	283	10 (4%)	395	19 (5%)	372	41 (11%)
7.5-<8.0% (58-<64 mmol/mol)	214	9 (4%)	410	15 (4%)	341	14 (4%)	357	24 (7%)	375	30 (8%)
8.0-<9.0% (64-<75 mmol/mol)	420	19 (5%)	866	38 (4%)	596	36 (6%)	398	27 (7%)	397	35 (9%)
≥9.0% (≥75 mmol/mol)	380	25 (7%)	1370	79 (6%)	888	60 (7%)	265	36 (14%)	184	17 (9%)
Frequency of ≥1 Diabetic Ketoacidosis Event in Prior 3 Months [b]										
Overall	1313	31 (2%)	3183	113 (4%)	2445	96 (4%)	2143	43 (2%)	1976	22 (1%)
Insulin Delivery Method										
Pump	973	12 (1%)	2134	49 (2%)	1585	44 (3%)	1442	24 (2%)	1243	14 (1%)
Injections	317	17 (5%)	967	61 (6%)	817	51 (6%)	656	17 (3%)	706	8 (1%)

CGM Status										
CGM user	414	4 (1%)	584	9 (2%)	424	9 (2%)	684	5 (1%)	577	1 (<1%)
CGM non-user	899	27 (3%)	2599	104 (4%)	2021	87 (4%)	1459	38 (3%)	1399	21 (2%)
Most Recent HbA1c										
<7.0% (<53 mmol/mol)	96	0	174	1 (1%)	257	2 (1%)	575	2 (<1%)	498	3 (1%)
7.0-<7.5% (53-<58 mmol/mol)	148	1 (1%)	268	3 (1%)	283	3 (1%)	395	2 (1%)	372	2 (1%)
7.5-<8.0% (58-<64 mmol/mol)	214	3 (1%)	410	2 (1%)	341	5 (1%)	357	2 (1%)	375	0
8.0-<9.0% (64-<75 mmol/mol)	420	5 (1%)	866	18 (2%)	596	9 (2%)	398	9 (2%)	397	8 (2%)
≥9.0% (≥75 mmol/mol)	380	20 (5%)	1370	83 (6%)	888	74 (8%)	265	25 (9%)	184	5 (3%)

a – A severe hypoglycemic event required loss of consciousness or seizure.
b – A diabetic ketoacidosis event diagnosed by a doctor and required an overnight hospitalization.